REMARKS

This paper is being filed in response to the non-final Office Action dated August 13, 2003 that was issued in connection with the above-identified patent application. Applicants also enclose herewith a Supplemental Information Disclosure Statement, a corresponding Form PTO-1449, copies of 3 documents, and the fee required pursuant to 37 C.F.R. §1.17(p) and §1.97(c)(2). Applicants respectfully request reconsideration of the instant application in view of the amendments and remarks presented herein.

Claims 1-15 are pending. Claims 4, 12, 13, and 15 have been amended to correct minor typographical errors. Therefore, these amendments do not constitute new matter. Therefore, claims 1-15 will remain pending upon entry of the instant Amendment.

Claims 1-10, 12, and 14 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over U.S. Patent No. 5,842,845 issued to Soares et al. on January 9, 1996 (hereinafter "Soares") in view of Adams et al., 1995, *Nature* 377:3-174 (hereinafter "Adams"). The Examiner has alleged that Soares teaches a method of cDNA sequencing comprising all of the limitations of claim 1 except that Soares does not teach hybridizing and subtracting the homogenized cDNA library with probes corresponding to the previously sequenced clones. However, the Examiner has alleged that Adams teaches hybridizing and subtracting cDNA libraries with probes corresponding to the clones previously sequenced.

Applicants respectfully traverse this rejection and assert that the Examiner has not satisfied his burden to establish a *prima facie* case of obviousness. For a combination of references to render a claim obvious, the references themselves must teach or suggest **each** and **every** element of the claim. *See* MPEP § 2143.03. Moreover, the references themselves must provide the motivation to make the asserted combination. Thus, to establish a *prima facie* case

of obviousness, the Examiner must show that Soares and Adams together teach or suggest **each** and **every** limitation of the pending claims. *See* MPEP § 2142. Applicants respectfully assert that the Examiner has not demonstrated how either Soares or Adams teach or suggest either "homogenizing the cDNA original library according to a graded C_0t value" or "hybridizing and subtracting the homogenized cDNA library with said probes" as recited in claim 1.

The instant claims relate to a method of cDNA sequencing that involves creating an original cDNA library, subdividing the cDNA original library according to graded C_0t values, and modifying a subdivided ("homogenized") cDNA library by reducing the presence of overly abundant cDNA clones. This normalization may be accomplished by allowing a subdivided "homogenized" cDNA library to hybridize to an overly abundant cDNA clone, and separating the hybridized DNA from unhybridized cDNAs. According to the invention, this hybridization and subtraction may be repeated up to about 5,000 times and results in a subtracted library that, unlike the original, contains few if any clones of the subtracted sequence(s). A powerful feature of the instant invention over the prior art is that the combination of "homogenizing the cDNA original library according to a graded C_0t value" and "hybridizing and subtracting the homogenized cDNA library with said probes" surprisingly makes it possible to sequence more than 90% of an organism's genome.

Soares teaches a method of normalizing a cDNA library. However, Soares teaches neither homoginizing a cDNA library according to graded C_0t values (*e.g.* Soares claim 1 merely recites "melting and reassociating the purified partial duplexes to appropriate C_0t") nor subtracting the library with probes that are synthesized on the basis of sequence information obtained from selected clones. In withdrawing the prior anticipation rejection, the Examiner has evidently acknowledged that Soares teaches only **single pass** sequencing, not the systematic,

iterative sequencing and subtraction of the instant invention. However, the Examiner has alleged that Adams fills this gap. The Examiner has cited the first paragraph of page 6 of Adams as allegedly teaching hybridizing and subtracting cDNA libraries with probes corresponding to the overly-abundant clones. However, Applicants respectfully assert that Adams merely teaches identification of low abundance clones and completely fails to teach either homogenizing according to graded C_0t values or subtraction as recited by the instant claims.

Adams teaches that several libraries were identified as having one or more abundant species. *See* Adams, page 6, first paragraph, first sentence. Next, either the abundant cDNA or the entire cDNA library was labeled. *See* Adams, page 6, first paragraph, second sentence. Then, labeled probe was used to "screen **gridded arrays** of clones from the library." *See* Adams, page 6, first paragraph, third sentence (emphasis added). One of ordinary skill in the art would recognize that this means that phage or bacterial colonies bearing individual library clones were adhered to a substrate (*e.g.* nylon filter) and then allowed to hybridize with the abundant cDNA. Array loci where no hybridization was detected were identified and the corresponding phage or bacterial colonies were picked for sequencing. However, one skilled in the art would recognize that this "selection" does not involve actually modifying the cDNA library in any way. Specifically, Adams does not teach or suggest subtraction of the cDNA library such that the abundance of the targeted nucleic acid is reduced. Therefore, since neither Adams nor Soares teaches or suggests homogenization and subtraction of the cDNA library as recited by the instant claims, the Examiner has not met the burden imposed by MPEP § 2142. Accordingly, Applicants respectfully request withdrawal of the instant rejection.
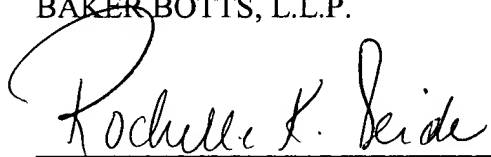
An objection has been raised against claims 11 and 13 (sic, and claim 15?) because they are dependent on a rejected independent base claim. Applicants respectfully request reconsideration of this objection in view of the foregoing remarks.

In summary, Applicants believe that all pending claims are in condition for allowance and respectfully solicit prompt favorable action.

Applicants enclose herewith the fee required under 37 C.F.R. §1.17(p) and §1.97(c)(2). Although Applicants do not believe that any additional fees are required with this paper, the Commissioner is hereby authorized to charge any fees occasioned by this submission not otherwise enclosed herewith to Deposit Account No. 02-4377. Please credit any overpayment of fees associated with this filing to the above-identified deposit account. A duplicate of this page is enclosed.

Respectfully submitted,

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November 13, 2003

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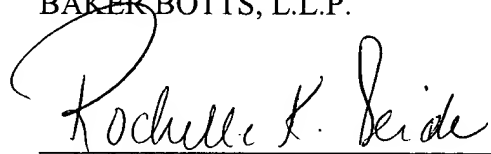30 Rockefeller Plaza
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Enclosures

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